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Evaluation of coronary artery disease as a risk factor for reticular pseudodrusen

Rachel V McCarter,¹ Gareth J McKay,¹ Nicola B Quinn,¹ Usha Chakravarthy,¹ Tom J MacGillivray,² Gavin Robertson,² Enrico Pellegrini,² Emanuele Trucco,³ Michelle C Williams,⁴ Tunde Peto,¹ Baljean Dhillon,² Edwin JR van Beek,⁵ David E Newby,⁴ Frank Kee,¹ Ian S Young,¹ Ruth E Hogg¹

¹Centre for Public Health, Queen's University Belfast, Belfast, UK

²VAMPIRE Project, Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh, UK

³VAMPIRE Project, Computing, School of Science and Engineering, University of Dundee, Dundee, UK

⁴Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK

⁵Clinical Research Imaging Centre, University of Edinburgh, Edinburgh, UK

Correspondence to

Dr Ruth E Hogg, Center for Public Health, Queen's University Belfast, Institute of Clinical Sciences, 1 Block A, Royal Hospital, Grosvenor Road, Belfast BT12 6BA, Northern Ireland; r.e.hogg@qub.ac.uk

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ABSTRACT

Purpose Reticular pseudodrusen (RPD) are a risk factor for late age-related macular degeneration (AMD). Associations between RPD and coronary artery disease (CAD) have been reported from small case-control studies. This study investigated the association of RPD within a predominantly CAD cohort.

Methods A subgroup of subjects from a multicentre randomised controlled trial of CT coronary angiography (CTCA) underwent ultrawide field (UWF) retinal imaging CAD determined by CTCA and was categorised as normal, non-obstructive or obstructive. Specific AMD features in UWF images were graded. Standardised grids were used to record the spatial location of AMD features, including RPD. Multivariate confounder adjusted regression models assessed the association between RPD and CAD.

Results The 534 participants were aged 27–75 years (mean 58±9 years; 425 (80%) ≥50 years) with a male preponderance (56%). Within the study sample, 178 (33%) had no CAD, 351 (66%) had CAD. RPD was detected in 30 participants (5.6%) and bilaterally in 23. Most participants with bilateral RPD had intermediate AMD 17 (74%). After adjustment for potential confounders (age, sex, drusen >125 µm, smoking status), multivariate analysis found no significant association between CAD and RPD (OR 1.31; 95% CI (0.57 to 3.01); p=0.52). A significant association was identified between RPD and intermediate AMD (OR 3.18; 95% CI (1.61 to 6.27); p=0.001).

Conclusion We found no evidence to support an association between CAD and RPD. RPD was strongly associated with intermediate AMD features.

Trial registration number NCT01149590, Post results.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of permanent blindness in the developed world with the most sight loss occurring in the late stages, namely geographic atrophy (GA) and choroidal neovascularisation (CNV).¹ Risk factors for progression from early to late AMD include advancing age, cardiovascular disease (CVD), obesity, cigarette smoking, ethnicity, hypertension, high cholesterol, genetic variants such as age-related maculopathy susceptibility 2 (ARMS2) gene, complement factor H (CFH) and apolipoprotein E (ApoE) gene and inflammatory markers such as

C-reactive protein.² Recently, reticular pseudodrusen (RPD) have been shown to be an important independent risk factor for progression to both GA^{3,4} and CNV.^{3,5} In addition, various risk factors have been reported to be associated with RPD including advancing age, female gender, smoking, ARMS2, complement component 3 (C3), *vascular endothelial growth factor A* (VEGFA) and CFH genetic variants.^{6–8}

RPD is a subtype of AMD associated with subretinal drusenoid deposits (SDD) and is located between the retinal pigment epithelium (RPE) and the inner ellipsoid zone.⁶ Associations between RPD, SDD, reticular macular disease and coronary artery disease (CAD) have been reported from small case-control studies. The acronyms and associated full titles are mentioned here in order to avoid any confusion. In particular, the term SDD is preferred for the actual physical deposits as first recognised within histopathology by Curcio *et al.*⁹

In association with the selection of image modality, variations in specific definitions of RPD have also led to substantial differences in reported prevalence rates. Initial reports of the association came from data collected on AMD cohorts recruited in hospital eye clinics and reported high prevalences ranging from 29% to 52%.^{6,10,11} Data from population-based studies are limited and show large variation, such as 0.4% from the Melbourne Collaborative Cohort study to 4.9% in the Rotterdam study and 13% in the Alienor study.^{7,8,12} Such varying estimates might be attributed to the different imaging and grading protocols used.

The strong association between RPD and a thin choroid has prompted a spate of small studies that have sought associations between RPD and CVD.^{13–17} Cymerman *et al* reported on a small prospective cohort of patients with no known retinal disease recruited from a cardiovascular clinic; 23 participants with CAD had a higher frequency of RPD compared with 15 who did not have CAD.¹³ A review by Rastogi and Smith¹⁴ on the association between AMD, RPD and CVD highlighted studies reporting an association between RPD and hypertension and angina.^{15–18} Smith and colleagues hypothesised that the increased mortality from systemic-vascular disease that affects men more severely compared with women, may account for the higher proportion of women with RPD that has been observed in various population-based studies.¹⁸ Notably, this review



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highlighted the potential importance of large prospective cohort studies sampling participants >45 years with and without CAD to identify RPD development and potential associations.¹⁴

A substudy of the SCOT-HEART (SH) trial that incorporated only ultrawide field (UWF) retinal imaging offered a unique opportunity to explore the relationship between CAD and RPD. The use of wide field technology to evaluate the retinal fundus offered an additional advantage as RPD is commonly located in the retinal arcades and beyond.¹⁵ To date, there is one study that has estimated RPD prevalence that has included central and peripheral retinal locations.¹⁹ In this study, RPD were present in 15% of subjects with AMD in zone 2, but none in the controls, a difference that was significant. However, the sensitivity of UWF to detect RPD has not been established. We therefore first validated the methodology using images from a population-based epidemiological study (the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA)) which captured UWF, colour fundus photography (CFP), infrared (IR) and autofluorescence (AF) images of the retina, and subsequently used the SH trial substudy UWF images to explore the relationship between RPD and CAD.

MATERIALS AND METHODS

Validation of detection of RPD by UWF imaging

Nine hundred consecutive participants were selected from the NICOLA study. CFP was performed on the Canon CX-1 Digital Fundus Camera (Canon USA, Melville, NY, USA). Stereoscopic pairs centred on the optic disc and macula were captured. CFP images were viewed and graded using the Oculab program (Digital Healthcare Oculab, V3.7.98.0; Emis Health, Leeds, UK). UWF retinal imaging was performed on the Optos Tx200 Scanning Laser Ophthalmoscope (Optos, Dunfermline, UK) using both colour and AF acquisition modes. Images were viewed and graded using the Optos V² Vantage Pro software (V2.9.4.2).

UWF images were graded for the presence or absence of RPD by a trained single grader who was not involved in any other grading procedures with quality assurance and reviewed by a retina specialist (UC). All available imaging modalities were used to determine the presence of RPD. This included *en face* images of colour, multicolour, AF and IR. In addition, high-resolution optical coherence tomograms were also scrutinised for the presence of SDD. The image grading was undertaken by trained graders in the network of UK Reading Centres (NetwORC UK) for the presence or absence of RPD. Detection of RPD on any modality was taken as evidence of presence of this feature. Sensitivity and specificity of the UWF imaging in detecting RPD compared with the RPD detected from the NICOLA cohort's *en face* and tomographic images were computed.

The SH study and sample

The SH trial (ClinicalTrials.gov, number NCT01149590) was a multicentre randomised controlled trial undertaken in Scotland (2010–2014) on 4146 participants, aged 18–75 years, drawn from 12 cardiology clinics across Scotland.²⁰ The main aim of the study was to determine the role of multidetector CT in the diagnosis and management of patients attending rapid access chest pain clinics. Participants were randomly assigned to either standard care (control intervention) or standard care and the CT coronary angiography (CTCA) and calcium scores (intervention). CAD was categorised in the SH study as: (1) obstructive CAD, atherosclerotic plaque encompassing a luminal cross-sectional area of $\geq 70\%$ in at least one major epicardial vessel; (2) non-obstructive CAD, either atherosclerotic plaque encompassing a luminal cross-sectional area of <70% but >10% in at

least one major epicardial vessel, or a calcium score >400 AU (Agatston units) or >90th percentile for age and sex; or (3) minimal or no CAD. Non-obstructive disease was further subdivided into mild (10%–50% luminal cross-sectional area) or moderate (50%–70% luminal cross-sectional area) stenosis. At two sites (Edinburgh and Dundee), consecutive patients were approached to undergo UWF imaging immediately before or after undergoing CTCA. We assessed 534 participants from a substudy of SH who had UWF imaging captured using two Optos P200C Scanning Laser Ophthalmoscopes (Optos) in addition to the normal study procedures at two sites (the Clinical Research Imaging Centre in Edinburgh and the Clinical Research Centre Dundee).²¹

Image grading in SH

Specific features of AMD in UWF images were graded for AMD characteristics (increased pigment, decreased pigment, drusen, maximum drusen size, RPD, GA and CNV) and other peripheral abnormalities using the 'Study-specific Grading Procedures for OPERA Study' guidelines (November 2013).²² The Optos software used a modified Studies of Ocular Complications of AIDS (SOCA) Optos PERipheral RetinA study (OPERA) grid (figure 1) which was divided into three zones: zone 1 (posterior pole), zone 2 (extends from Z1 to a circle through the ampullae of the vortex veins) and zone 3 (extends from Z2 to the outer periphery). The Manchester grid was superimposed on the SOCA grid to estimate the ungradable areas (figure 2). In accordance with the OPERA guidelines, at least 50% of the subfield should be visible to grade; if <50% of the subfield was visible, it was graded as 'Cannot Grade.' If AMD characteristics and other pathologies were present in a Cannot Grade subfield, and if the grader was $\geq 90\%$ certain the lesion was present, then grading was ascribed. Drusen presence was graded as follows: absent; questionable; 1–5 drusen; 6–20 drusen; >20 drusen or cannot grade. The maximum drusen size was graded as follows: <125 μm ; $\geq 125 \mu\text{m}$, <250 μm distinct; $\geq 125 \mu\text{m}$, <250 μm indistinct; $\geq 250 \mu\text{m}$ distinct; $\geq 250 \mu\text{m}$ indistinct or cannot grade. RPD was graded as follows: absent; questionable; <25% of subfield; 25%–49% of subfield; 50%–74% of subfield; $\geq 75\%$ of subfield or cannot grade. RPD were defined as yellow interlacing networks ranging from 125 μm to 250 μm in width or lesions that occurred in regular well-defined domains (figure 3). Images in which RPD were questionable were arbitrated by a retina specialist (UC).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics V.20. Intraobserver agreement was calculated after 1 in 20 of the images was randomly regraded for RPD and drusen using kappa (k) statistics, which express the extent of agreement beyond chance. The interpretation of the k statistic was as follows: 0, no agreement; 0–0.2, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.8, substantial agreement; and >0.81, almost perfect agreement.²³

Univariate analysis (χ^2 test or Fisher's exact test for categorical variables and independent t-test for continuous variables) was used to examine differences in the demographic characteristics of participants according to presence or absence of RPD. General estimating equations (GEE) which enabled data from both eyes to be included were used to examine the association between RPD and CAD while accounting for other factors identified as significant from the univariate analysis.

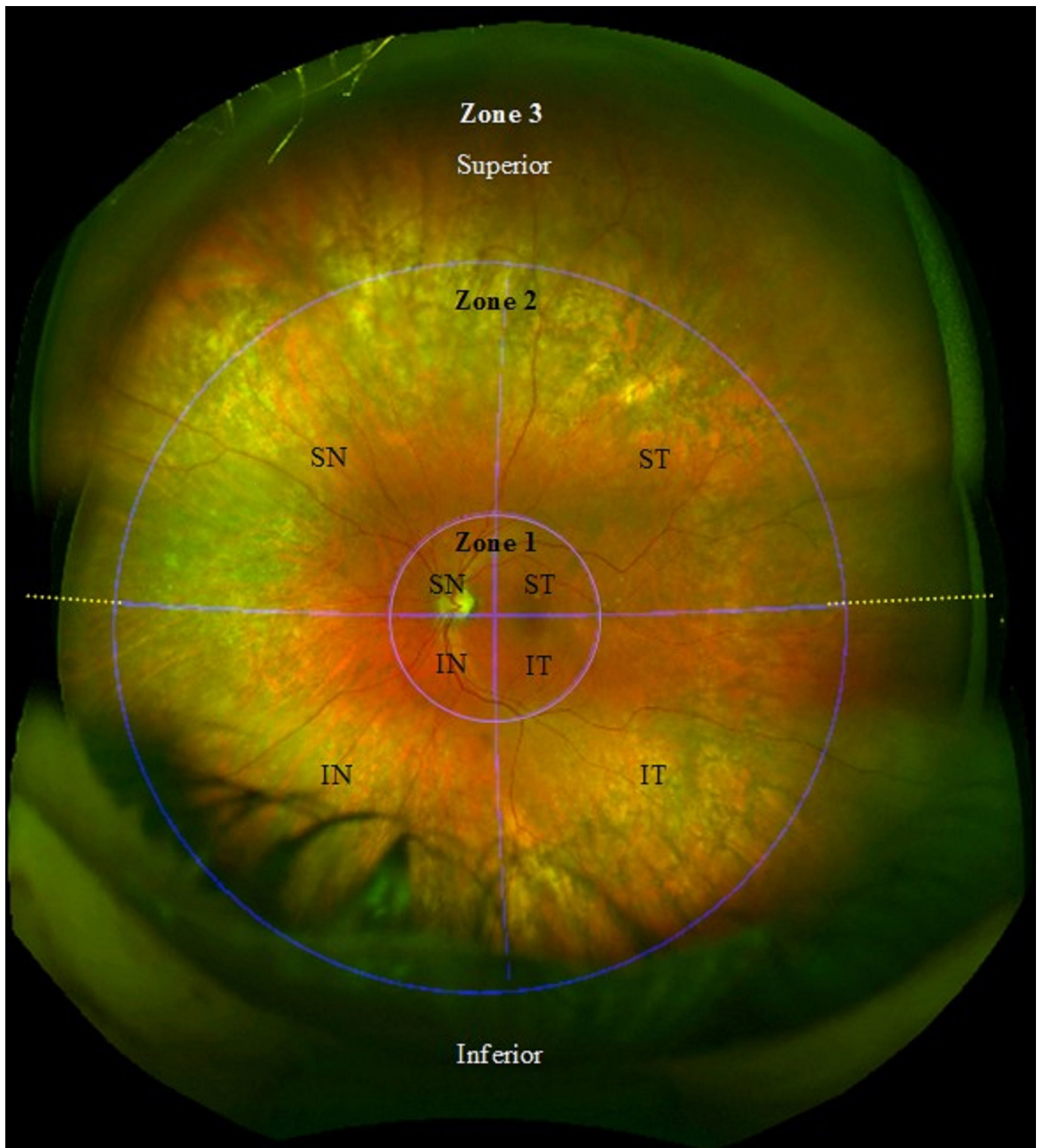


Figure 1 The modified Studies of Ocular Complications of AIDS grid used on the Optos software. Z1 and Z2 are each divided into four quadrants: superonasal (SN), superotemporal (ST), inferotemporal (IT) and inferonasal (IN). Z3 is divided into two hemispheres (superior, inferior) using a visual extension of the horizontal cross line (yellow dashed lines). (Taken from the Study-specific Grading Procedures for Optos PEripheral RetinA study, University of Wisconsin (2013)).²²

RESULTS

Validation study

The sensitivity and specificity of UWF were compared with *en face* and tomographic multimodal images in the detection of RPD. Of the images acquired from the 900 consecutive participants included in the validation study, UWF imaging detected eight participants with reticular drusen (two unilateral and six bilateral;

100% sensitivity). Multimodal imaging (colour, multicolour, IR and AF and optical coherence tomography) detected RPD in seven of those which were seen on *en face* images. The specificity of the UWF imaging was 99.9%. In one case, the UWF imaging detected RPD beyond the field of view captured by the combination of retinal imaging (figure 4). The positive predictive value was calculated at 87.5% and the negative predictive value was 100%.

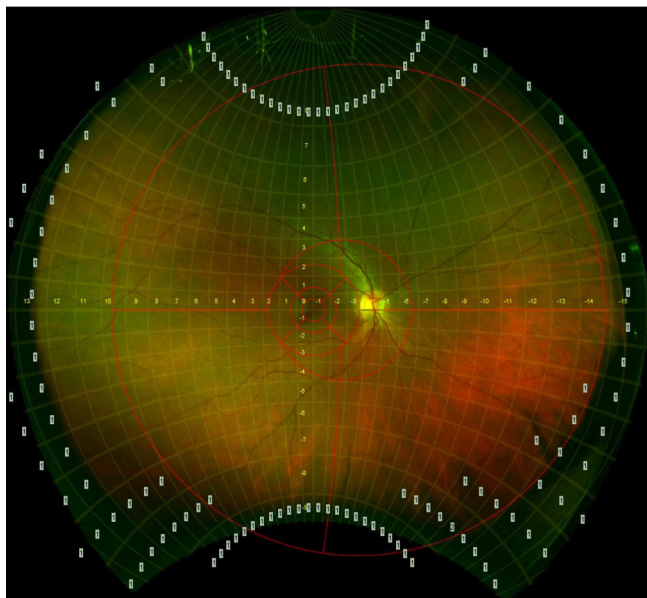


Figure 2 Optos ultrawide field retinal image grading grids for specific age-related macular degeneration characteristics. The SOCA grid is divided into three zones: zone 1 (posterior pole), zone 2 (extends from Z1 to a circle through the ampullae of the vortex veins) and zone 3 (extends from Z2 to the outer periphery). The Manchester grid was superimposed onto the SOCA grid to assess the ungradable areas. SOCA, Studies of Ocular Complications of AIDS.

Participant characteristics in SH study

Table 1 summarises SH study participant characteristics. In total, 534 individuals had UWF retinal images captured. Two participants (four eyes) proved difficult to scan and images were not obtained. This left 532 pairs of eyes for grading. The mean age was 58 years (range=27–75, SD 9.5) with 425 (80%) aged over 50 years. There were 299 men (56%). A total of 178 (33%) had no CAD, 351 (66%) had CAD present, while 182 (34%) had hypertension and 42 (24%) had no CAD or hypertension.

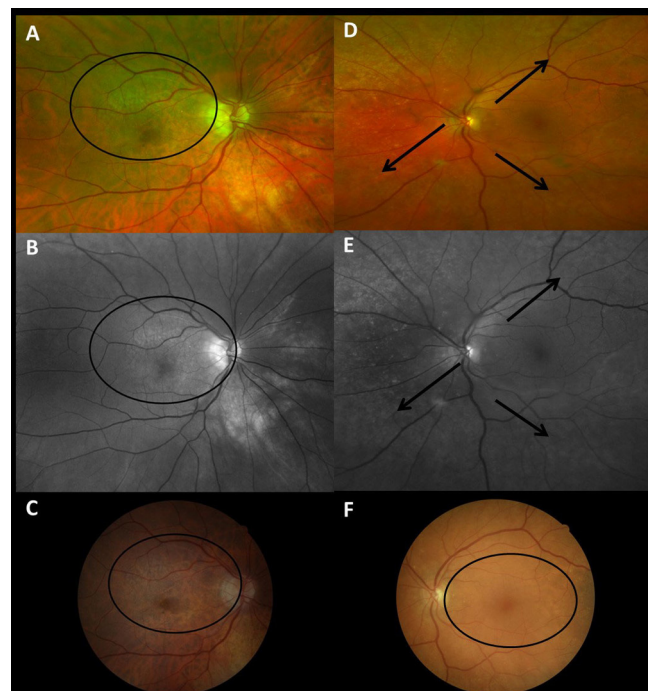


Figure 4 The RPD interlacing pattern on both the UWF and fundus camera image. (A) UWF pseudocolour image showing RPD (black circle). (B) UWF green laser imaging with RPD visible within the black circle. (C) Fundus camera image with RPD within the black circle. (D) UWF pseudocolour image with arrows pointing to areas of RPD. (E) UWF green laser imaging with arrows annotating areas of RPD. In this case, RPD was detected beyond the field of view of colour fundus photography. (F) Corresponding fundus camera image with no readily visible RPD within the black circle. RPD, reticular pseudodrusen; UWF, ultrawide field.

The intragrader agreement illustrated in **table 2** gives the kappa range for the AMD features: for the presence of RPD it ranged from: 0.62–0.76; for drusen: 0.58–0.64, maximum

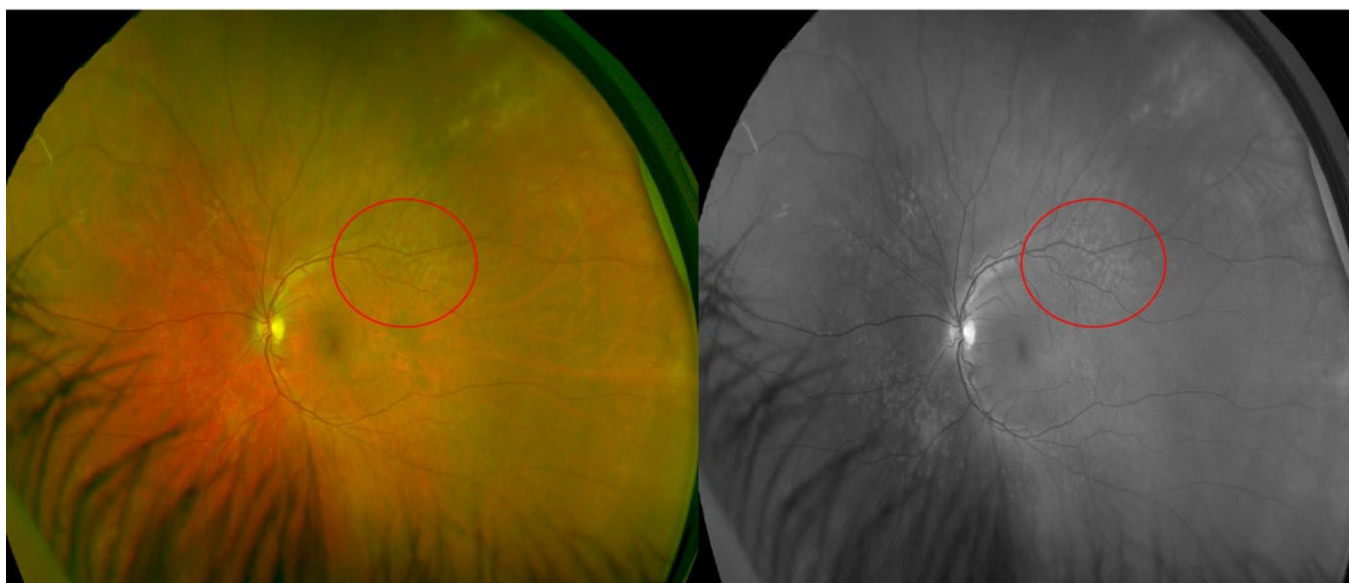


Figure 3 Optos UWF retinal image illustrating RPD. The appearance of RPD on UWF is described as an interlacing reticular pattern, which appear superiorly in the outer macula and extend circumferentially and further. RPD, reticular pseudodrusen; UWF, ultrawide field.

Table 1 Summary statistics for study participants

	All participants n=534	Reticular pseudodrusen (one or both eyes)		p
		Absent n=504	Present n=30	
Age				0.76
Mean (SD)	58 (10)	58 (9)	59 (12)	
Sex (%)				0.57
Male	299 (56)	284 (56)	15 (50)	
Female	235 (44)	220 (44)	15 (50)	
Body mass index				0.19
Mean (SD)	30 (7)	30 (7)	28 (6)	
CAD diagnosis (%)				0.71
None	178 (33)	168 (33)	10 (33)	
Non-obstructive to mild	114 (21)	105 (21)	9 (30)	
Non-obstructive to moderate	87 (16)	84 (17)	3 (10)	
Obstructive CAD	150 (28)	142 (28)	8 (27)	
Missing	5 (1)	5 (1)	0 (0)	
CAD (%)				0.99
Absent	178 (33)	168 (33)	10 (33)	
Present	351 (66)	331 (66)	20 (67)	
Missing	5 (1)	5 (1)	0 (0)	
Assign score				0.56
Mean (SD)	18 (12)	18 (12)	17 (11)	
Coronary artery calcium score				0.67
Mean (SD)	314 (805)	310 (814)	376 (634)	
Hypertension (%)				0.84
No	346 (65)	327 (65)	19 (63)	
Yes	182 (34)	171 (34)	11 (37)	
Missing	6 (1)	6 (1)	0 (0)	
Diabetes (type 1 or 2) (%)				0.76
No	483 (90)	455 (90)	28 (93)	
Yes	51 (10)	49 (10)	2 (7)	
Drusen >125 µm (%)				0.01
Absent	330 (62)	319 (63)	11 (37)	
Present	201 (38)	183 (36)	18 (60)	
Missing	3 (1)	2 (1)	1 (3)	
Smoking history (%)				0.25
Never	256 (48)	244 (48)	12 (40)	
Ex-smoker	193 (36)	183 (36)	10 (33)	
Current smoker	85 (16)	77 (15)	8 (27)	

CAD, coronary artery disease.

drusen size: 0.55–0.62, increased pigment: 0.54–0.61, decreased pigment: 0.55–0.62; for GA: 0.62–0.76; for neovascular AMD: 0.57–0.66 and for peripheral abnormality: 0.55–0.59 within zones 1–3. For the lesions which were absent in the cohort the discordance in the grading originated from a change of grade of feature absent to ungradable between the two gradings.

Prevalence of RPD and AMD features in the SH study

RPD was present in one or both eyes of 30 participants (5.6%) and bilateral in 23 participants (4.3%). Intermediate AMD was present in 201 participants (38%). Participants with RPD ranged in age from 33 to 75 years (mean 59) and there were equal numbers of men and women. The other AMD features graded as present in the participants were as follows: 352 (66%) had hyperpigmentation, 55 (10%) had hypopigmentation, 2 (0.4%) had unilateral GA, none of the participants was classified

Table 2 Intragrader agreement for the individual AMD phenotypes

AMD characteristic	Kappa range		
	Zone 1	Zone 2	Zone 3
Neovascular AMD	0.66	0.57	0.61
Increased pigment	0.59	0.54	0.61
Decreased pigment	0.66	0.55	0.62
Geographic atrophy	0.66	0.76	0.62
Drusen	0.59	0.64	0.58
Maximum drusen size	0.60	0.62	0.55
Reticular pseudodrusen	0.67	0.76	0.62
Peripheral abnormality	NA	0.59	0.55
Presence of other pathology (all zones)	0.62		

AMD, age-related macular degeneration; NA, not applicable.

as having neovascular AMD and 183 (34%) showed other non-AMD peripheral abnormalities.

Association of CAD with RPD

CAD was present in 20 participants and absent in 10 participants with RPD; however, no statistically significant association between RPD and CAD was found on either the unadjusted or adjusted GEE model ($p>0.05$, table 3). With respect to associations between RPD and other early AMD features, a strong association was noted with intermediate AMD in the fully adjusted model (OR 3.18; 95% CI (1.61 to 6.27); $p=0.001$). Eighteen participants had both RPD and intermediate AMD, while 11 participants had RPD alone without evidence of soft drusen.

DISCUSSION

We believe that our study is the first to report on the prevalence of RPD using UWF retinal images in patients with confirmed CAD. Contrary to previous reports, our study did not reveal a significant association between RPD and CAD.^{13–16 18} Detection of RPD was based on retinal wide field imaging and was graded using standardised protocols. We validated the ability of UWF colour images to detect RPD by checking agreement within a set of images acquired using multimodal technology and demonstrated that UWF was reliable, reproducible and robust. Our findings are in accordance with population-based studies and some of the clinical cohorts that did not report significant associations between RPD and CAD or hypertension.^{6–8 12 24} In fact, the prevalence of RPD observed in the current SH study (30 out of 534 participants—5.6%) is similar to that reported by the population-based Rotterdam study (4.9%),⁷ providing additional support for the view that CAD is not associated with an increased prevalence of RPD. Interestingly, Zarubina *et al* studied patients from primary care eye clinics with and without AMD, and using multimodal imaging and strict criteria found that the prevalence of SDD in subjects without AMD was 23%. However, using expanded criteria, Zarubina *et al* discovered that the prevalence of SDD on any modality, closest to that of the current study, rose to 69% in subjects with a mean age of ~68 years. In comparison, the population in the current study had a mean age of ~58 years, and an SDD prevalence of only 5.6%. This is a large difference in prevalence, as Zarubina *et al* used SD-OCT, whereas this study only used UWF, and RPD is better detected on SD-OCT, so it would be expected to have a lower prevalence on UWF.²⁴

While 80% of participants were aged over 50, a common age restriction for many AMD studies, interestingly eight participants with RPD were aged under 50, the youngest aged 33.

Table 3 Investigation of CAD as a risk factor for reticular pseudodrusen using generalised estimating equations.

	Unadjusted model			Age and sex adjusted			Multivariate adjusted*		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
CAD	1.30	0.58 to 2.92	0.52	1.33	0.57 to 3.11	0.52	1.31	0.57 to 3.01	0.52
Age				1.01	0.95 to 1.07	0.78	1.00	0.95 to 1.06	0.92
Sex				1.51	0.67 to 3.40	0.32	1.40	0.62 to 3.14	0.42
Drusen >125 µm							3.18	1.61 to 6.27	0.001

*Multivariate model was adjusted for age, sex and smoking status.

CAD, coronary artery disease.

Of these, four (50%) also had evidence of intermediate AMD whereas the rest had no other features of AMD present. If, as has been proposed, the primary lesion is vascular (choroidal insufficiency), then as the disease progresses the development of SDD may follow. It is possible that this may be one explanation for the findings of fewer SDD within a younger population. In the overall sample, seven participants had RPD without any other AMD features similar to previous observations,⁷ which may reflect a different phenotype given that RPD have been reported in other retinal diseases such as Sorsby fundus dystrophy, pseudoxanthoma elasticum and acquired vitelliform lesions.^{25–27} Given the rarity of these participants, it is likely that studies of large sample size or pooled analyses across studies will be required to improve our understanding of the relevance of these isolated RPD.

The RPD phenotype in AMD has been shown to be associated with choroidal thinning^{28–33} and thus it has been suggested that RPD arise as a consequence of choroidal vascular pathology such as age-related atherosclerosis. Interestingly, Leisy *et al* recently found an association between the RPD phenotype and renal dysfunction.³⁴ However, we were unable to establish a relationship in a large population with a diagnosis of CAD that was established using robust methodology and which constitutes an important marker for systemic vascular disease. Therefore, we contend that the pathogenesis of RPD remains unresolved and we suggest that the outer photoreceptor mosaic may be the source of this material which in turn is a consequence of RPE degeneration with withdrawal of trophic/survival factors to the photoreceptors.

This is only the second study, to our knowledge, that used UWF imaging for the evaluation of RPD.¹⁹ Using the NICOLA image repository we confirmed the reliability of this approach to detect reticular drusen which have been observed when using other *en face* modalities such as IR or AF imaging. Nonetheless, we are of the view that as with other *en face* modalities, UWF imaging also underestimates the prevalence because the earliest stages of the SDD phenotype are best appreciated on high-resolution SD-OCT.³⁵ Stage 1 SDD is defined by the dispersed nature of the deposits of granular hyper-reflective material that is present in the outer retina in the region of the photoreceptors' inner and outer segments (the IS/OS boundary) and the RPE. A characteristic reticulated pattern accompanies stages 2 and 3, which has been attributed to focal deposits that cause marked alterations to the IS/OS boundary and thus become detectable by *en face* imaging.³⁵ Currently, it is accepted that detection of RPD is best when a multimodal approach, combining IR, AF and SD-OCT, is used.^{12–36} We were however reassured by the validation study which demonstrated the benefit of the increased field of view provided by UWF imaging. We also noted that RPD was evident in at least one participant in an area of the retinal fundus that is typically

not included in colour images (35° or 45°) or OCT, raising the possibility of under ascertainment when the field of examination is restricted to the central fundus.

A potential limitation of this study is the choice of controls as all participants (cases and controls) were recruited from cardiology clinics. However, control status was only assigned following an extensive and robust clinical examination, CTCA and calcium scores. This cohort may therefore have characteristics that are dissimilar from that of a random population-based sample. Even though we adjusted for age, sex and smoking habit, some of the established AMD risk factors, such as diet, and genetic risk, were not available and therefore residual confounding may have been present. However, concerns over residual confounding are less worrisome, given the absence of the finding of a positive association between CAD and RPD.

In conclusion, our study does not support previously reported associations with CAD. As with other studies, we observed the strong association with the hallmark feature of classical drusen which is recognised as early AMD. Our findings highlight the necessity for other studies in this age group with improved phenotyping of the ocular fundus as well as vascular disease in other organ systems. Data from large and well-characterised longitudinal population-based studies with multimodal imaging will be required. In addition, pooled analyses of multiple studies to improve statistical power may help untangle the complexity of the risk factors and subphenotypes involved.

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Contributors The corresponding author and all of the authors have made the following contributions: (1) conception and design, or acquisition of data, or analysis and interpretation of data; (2) drafting the article and/or reviewing, revising it critically for important intellectual content; (3) final approval of the version to be published. REH: (1), (2), (3). RVM: (1), (2), (3). GJM: (1), (2), (3). NBQ: (1), (2), (3). UC: (2), (3). TJM: (1), (3). GR: (1), (3). EP: (1), (3). ET: (1), (3). MCW: (1), (3). TP: (1), (3). BD: (1), (3). EJRvB: (1), (3). DEN: (1), (3). FK: (1), (3). ISY: (1), (3).

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Competing interests FK and ISY are the study principal investigator and study originator of NICOLA.

Patient consent Obtained.

Ethics approval Research Ethics Committee, Scotland.

Provenance and peer review Not commissioned; externally peer reviewed.

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